REMARKS

The present application was originally filed with 7 Claims. In the Restriction Requirement mailed October 31, 2002, the Examiner restricted the Claims into two Groups, with Claims 1, 2-3, 4, 5-6 in Group I, and Claims 1, 4 and 7 in Group II. In a Response filed January 16, 2003, Applicants elected the Claims in Group I with traverse, and cancelled Claim 7. Applicants also elected the species "enzymes" as recited in Claim 6. Applicants respectfully submit that as the species originally elected are patentable, the remaining species are likewise allowable. As of the date of the present Office Action, Claims 1-6 and 8 were pending, as Claim 8 was previously added.

In the present Office Action, Applicants note that the Examiner has removed his previous rejections and objections. However, the Examiner has set forth two new rejections. In the first rejection, the Examiner rejected Claims 1-6 and 8, under 35 U.S.C. §102(e), as allegedly being anticipated by Weidenhammer *et al.* (US Patent No. 6,379,897). The Examiner also rejected Claims 1-6 and 8, under 35 U.S.C. §102(e), as allegedly being anticipated by Caldwell *et al.* (US Patent No. 6,582,914). Applicants must respectfully disagree with the Examiner's rejections and arguments.

1) The Claims are Novel Over the Weidenhammer *et al.* Patent

The Examiner has rejected Claims 1-6 and 8, under 35 U.S.C. §102(e), as allegedly being anticipated by Weidenhammer *et al.* (US Patent No. 6,379,897). The Examiner argues that the Weidenhammer *et al.* Patent discloses methods for preparing a library of mutant nucleic acids. In particular, the Examiner argues that the Weidenhammer *et al.* Patent discloses preparing first and second oligonucleotides corresponding to a first and second desired mutation within a template nucleic acid and allowing them to hybridize to a template. In addition, the Examiner argues that this Patent discloses subjecting the mixture of primers to linear cyclic amplification to produce a library of mutant template nucleic acids. Furthermore, the Examiner argues that the Patent " . . . discloses that the primers can be completely random and thus would include discontiguous primers and also that the primers can bind to different mRNAs or different cDNAs which would also be discontiguous . . . ." (Office Action, page 4). The

Examiner also argues that the Patent discloses that both mutant and non-mutant oligonucleotides can be used. In addition, the Examiner argues that the Patent discloses oligonucleotides that are present in less than saturating conditions, that the "target" nucleic acid refers to a "gene" of interest, and that the "target protein can be any target that is expressed in cells, including IL-1, TGFβ2, IL6, etc." (Office Action, page 6).

Applicants must respectfully disagree with the Examiner's arguments and submit that the Claims are novel over the Weidenhammer *et al.* Patent. Applicants respectfully submit that the Weidenhammer *et al.* Patent is directed toward monitoring or detecting the relative amounts of mRNA in at least one biological sample. The methods involve isolating the mRNA of interest, amplifying mRNA transcripts to produce amplicons, hybridizing the amplicons to probes bound to a support, and then detecting the amounts of each amplicon bound to the probes. As stated in the Detailed Description, "[t]he methods described are designed to determine the abundance of target genes in a distinct polynucleotide population, particularly as compared to the abundance of those target genes within a different polynucleotide population." (col. 7, lines 27-32). Thus, in contrast to the Examiner's statement that Weidenhammer "discloses methods for preparing a library of mutant nucleic acids," (Office Action, page 3), Applicants respectfully submit that there is no aspect of the Weidenhammer *et al.* Patent that involves the production of mutant oligonucleotide libraries.

Applicants respectfully submit that the Examiner may have misunderstood the use of "chimeric oligonucleotides" in the Weidenhammer *et al.* Patent. As described in this Patent, the chimeric oligonucleotides are specific to each target of interest, in order to generate amplicons for the gene sequences of interest. As indicated "[t]hese oligonucleotides contain an RNA polymerase promoter sequence at the 5' end . . . [a]djacent to the RNA polymerase promoter site is a sequence specific to the target gene of interest . . . ." (col. 8, lines 55-63). Furthermore, the oligonucleotides may contain a marker, such as biotin (*See*, col. 8, line 67 through col. 9, line 1). In addition, "[t]he chimeric oligonucleotides are typically chose to represent targets that are known or suspected to be differentially expressed under the experimental conditions . . . or may represent targets for which no expression data are available." (col. 9, lines 16-20).

Applicants further respectfully submit that the Weidenhammer *et al.* Patent does not disclose the use of chimeric primers of any sort for the generation of mutant end-product genes of interest. Rather, the chimeric primers can be used to insert/create restriction enzyme recognition sites within the amplicons that contain the gene sequences of interest. Thus, unlike the presently claimed invention, the final end product of the Weidenhammer *et al.* Patent methods is not a final gene sequence of interest that has been mutated, rather it is an amplicon that contains the desired (unmutated) gene sequence of interest. Indeed, it would make no sense in the context of the Weidenhammer *et al.* Patent invention to generate mutant oligonucleotides for use in monitoring/detecting gene expression. Rather, it would seem that it would be necessary to ensure that the gene sequences of interest are **not** mutated, in order that the gene expression be detected under optimum conditions. If mutated gene sequences were used in the detection/monitoring methods of the Weidenhammer *et al.* Patent, it is likely that the specificity and affinity of the probes would be compromised, due to sequence differences. Thus, taken as a whole, the Weidenhammer *et al.* Patent *teaches away* from the presently claimed invention.

As reiterated by the Courts, the cited reference must identically describe each and every claim element in order to be a proper 102 reference (*See e.g., Atlas Powder v. E.I. duPont*, 224 U.S.P.Q. 409 (Fed. Cir. 1984), *Jamesbury Corp. v. Litton Industrial Products*, 225 USPQ 253 (Fed. Cir. 1985), *Richardson v. Suzuki Motor Co., Ltd.*, 868 F.2d 1226 (Fed. Cir. 1989), U.S. *cert. den.*, 493 U.S. 853 (1989)). As the Weidenhammer *et al.* Patent fails to teach the use of LCR to produce the desired end-product (*i.e.*, mutant oligonucleotide libraries), Applicants respectfully submit that the presently claimed invention is novel over the Weidenhammer *et al.* Patent. Because the independent Claim is novel over the Weidenhammer *et al.* Patent, Applicants respectfully submit that the dependent Claims are likewise novel over the Weidenhammer *et al.* Patent. Thus, Applicants respectfully request that this rejection be withdrawn and the pending Claims be passed to allowance.

2) The Claims are Novel Over the Caldwell *et al.* Patent

The Examiner has rejected Claims 1-6 and 8 under 35 U.S.C. §102(e), as allegedly being anticipated by Caldwell *et al.* (US Patent No. 6,582,914). In particular,

the Examiner argues that the Caldwell *et al.* Patent discloses methods for generating a library of oligonucleotides comprising a controlled distribution of mutations. In particular, the Examiner argues that the Caldwell *et al.* Patent discloses preparing a first and second oligonucleotide corresponding to a first and second desired mutation within a template nucleic acid and allowing them to hybridize to the template. In addition, the Examiner argues that the Caldwell *et al.* Patent discloses that the first and second oligonucleotides can be non-complementary. Furthermore, the Examiner argues that the Caldwell *et al.* Patent discloses subjecting the mixture of primers to linear cyclic amplification to produce a library of mutant template nucleic acids. The Examiner also argues that the oligonucleotides are discontiguous, and can be present in less than saturating conditions, as well as non-mutagenic primers, protein products such as enzymes, hormones, vaccines, antibodies, etc. The Examiner also argues that the Caldwell *et al.* Patent discloses more than two non-mutagenic primers.

Applicants must respectfully disagree with the Examiner's arguments and submit that the pending Claims are novel over the Caldwell *et al.* Patent. While the Examiner is correct in stating that the Caldwell *et al* Patent discloses methods for generating oligonucleotide libraries and the methods favor the production of varied combinatorial mutants, the methods are very different from those of the pending Claims. In contrast to the presently claimed invention, which relies upon the linear cyclic amplification (LCR) method, the Caldwell *et al.* Patent clearly relies upon PCR (*i.e.*, the polymerase chain reaction). There are many references in the Caldwell *et al.* Patent, including in the Claims, that indicate that the method utilized by the Caldwell *et al.* invention involves PCR (*See e.g.*, col. 2, line 58; col. 3, line 15; col. 3, line 60; col. 4, line 13; col. 10, lines 25-29; and Claim 1, etc.). Furthermore, the definition of "amplification" in the Caldwell *et al.* Patent only includes PCR (*See*, col. 7, lines 32-38). Indeed, overall, the Caldwell *et al.* Patent emphasizes PCR, and the only Example describes the use of PCR.

As known to those in the art and as indicated in the present Specification, PCR and LCR are very different (*See e.g.*, page 8, line 25, through page 9, line 5). Unlike PCR, in which the end-products of the reaction accumulate in an exponential manner, in LCR, the end-products of the reaction accumulate in a linear manner. Applicants

respectfully submit that the Examiner may have misunderstood the description in the Caldwell *et al.* Patent of the production of "long products" or "megaprimers" as being LCR. Applicants respectfully submit that as described in Caldwell *et al.*, these long products/megaprimers act as templates for one or the other of the oligonucleotide primers during subsequent PCR cycles and produce molecules of the desired sequence (*i.e.*, the end-products of the reaction) (col. 11, lines 8-11). "These molecules will also function as templates for one or the other of the oligonucleotide primers, producing further desired product and thus a chain reaction can be sustained which will result in the accumulation of desired product at an exponential rate relative to the number of cycles." (col. 11, lines 11-16). This is very different from the LCR method, in which the **desired end-product** accumulates at a linear rate relative to the number of cycles. In order to more clearly define the claimed invention, Applicants have deleted the word "template" in step (e) of Claim 1. Thus, it is clear that the desired end-product of the LCR method of the presently claimed invention is a library of mutant nucleic acids (*i.e.*, a library of mutant nucleic acids). Support for this amendment is found throughout the Specification, as it is clear that it is intended the end-product of the method be a library of mutant oligonucleotides. Thus, no new matter is added by this amendment. Of course, this library would find use in additional rounds of LCR in which new libraries are generated (*i.e.*, they would be useful as templates in step (a) of Claim 1).

Thus, Applicants respectfully submit that the Caldwell *et al.* Patent does not disclose nor even suggest the LCR method used to produce mutant libraries as presently claimed. As indicated above and repeatedly reiterated by the Courts, the cited reference must identically describe each and every claim element in order to be a proper 102 reference (*See e.g.*, *Atlas Powder v. E.I. duPont*, 224 U.S.P.Q. 409 (Fed. Cir. 1984), *Jamesbury Corp. v. Litton Industrial Products*, 225 USPQ 253 (Fed. Cir. 1985), *Richardson v. Suzuki Motor Co., Ltd.*, 868 F.2d 1226 (Fed. Cir. 1989), U.S. *cert. den.*, 493 U.S. 853 (1989)). As the Caldwell *et al.* Patent fails to teach the use of LCR to produce the desired end-product (*i.e.*, mutant oligonucleotide libraries), Applicants respectfully submit that the presently claimed invention is novel over the Caldwell *et al.* Patent. Because the independent Claim is novel over the Caldwell *et al.* Patent, Applicants respectfully submit that the dependent Claims are likewise novel over the Caldwell *et al.* Patent.

Thus, Applicants respectfully request that this rejection be withdrawn and the pending Claims be passed to allowance.

CONCLUSION

In light of the above remarks, the Applicant believes that the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-5838.

Respectfully submitted,

Date: April 9, 2004

Kamrin T. MacKnight
Registration No. 38,230

Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94304
Tel: 650-846-5838
Fax: 650-845-6504